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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,723	12/17/2001	Kenya Shitara	249-243	6052

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NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,723	SHITARA ET AL.	
	Examiner	Art Unit	
	James L Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12172001; 03292002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

Applicant's election of Group I, claims 1-31, in the reply filed on 18 August 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, claims 32-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The disclosure is objected to because of the following informalities: the specification is replete with grammatical, idiomatic, and spelling errors and should be carefully revised. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 5-8, 15-18, and 26-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies as claimed are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the claimed cell line; the cell lines which produce the chemically and functionally distinct antibodies claimed; and/or, the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it

would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the cell lines as claimed. A suitable deposit of the hybridomas and plasmids required to make the antibodies as claimed would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) the deposits were viable at the time of deposit; and,
(e) the deposits will be replaced if they should ever become non-viable.

Applicant is also reminded that information regarding the deposits, such as the name and address of the depository, in addition to the accession numbers of the deposits and the date(s) of the deposits, **must** be added to the specification by means of filing an amendment as required by 37 CFR §1.809(d).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-9, 11-20, and 25-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 4-9, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

Claims 11-20 provide for the use of a substance, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. A method claim should also clearly state each component used in the method and the relationship of the various components. A method claim should also conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claims 14-19, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

In claims 25-30, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,
> except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claims 1-31 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Shitara et al. (EP 0,882,799).

Shitara et al. disclose the anti-VEGF receptor Flt-1 monoclonal antibodies KM1730, KM1731, KM1732, KM1748, and KM1750 (see e.g. page 7), and their use in detection assays for, for example, cells expressing the receptor on the cell surface (see e.g. page 8) or in diagnostic assays for, for example, tumors or rheumatoid arthritis.

Claims 1, 11, 21, and 22 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Barleon et al. (Blood 87: 3336, 1996).

Barleon et al. teach detection of VEGF receptor Flt-1 on the surface of human monocytes with radiolabelled VEGF.

Claims 1, 11, 21, and 22 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Clauss et al. (J. Biol. Chem. 271: 17629, 1996).

Clauss et al. teach detection of VEGF receptor Flt-1 on the surface of human monocytes with radiolabelled VEGF.

Claims 1-31 are rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by Shitara et al. (U.S. Pat. No. 6,617,160).

Shitara et al. disclose the anti-VEGF receptor Flt-1 monoclonal antibodies KM1730, KM1731, KM1732, KM1748, and KM1750 (see e.g. col. 6), and their use in detection assays for, for example, cells expressing the receptor on the cell surface (see e.g. cols. 12-13) or in diagnostic assays for, for example, tumors or rheumatoid arthritis (see e.g. col. 11).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either of Shitara et al. (EP '799) or Shitara et al. (US '160) in view of Kendall et al. (U.S. Pat No. 5,861,484) and either of Clauss et al. or Barleon et al.

The teachings of Shitara et al. (EP '799), Shitara et al. (US '160), Clauss et al., or Barleon et al. are as set forth above and differ from the invention as instantly disclosed in not specifically teaching detection of VEGF Flt-1 receptor on monocytes with anti-Flt-1 antibodies.

Kendall et al. teach (see e.g. col. 6) that VEGF receptor expressing cells can be detected by the notoriously old and well known alternatives of binding with radiolabelled VEGF or with anti-VEGF receptor antibodies.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used the anti-Flt-1 receptor antibodies of Shitara et al. (EP '799) or Shitara et al. (US '160) in a reagent for detection of this receptor on

monocytes because monocytes were known to express the receptor from radiolabelled VEGF binding assays (Clauss et al. or Barleon et al.), the references of Shitara et al. (EP '799) or Shitara et al. (US '160) teach their antibodies for determinations of receptor expressing cells, and one would have been motivated to detect the receptor on monocytes with the anti-Flt-1 antibodies of Shitara et al. (EP '799) or Shitara et al. (US '160) in view of the generic teachings of these references to do so with an extremely reasonable expectation of success in view of the known presence of the receptor on these cells (Clauss et al. or Barleon et al.) and the notoriously old and well known substitution of antibody binding for radiolabelled ligand binding to detect this receptor on expressing cells taught in Kendall et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either of Shitara et al. (EP '799) or Shitara et al. (US '160) in view of Kendall et al. (U.S. Pat No. 5,861,484) and either of Clauss et al. or Barleon et al. for the reasons as set forth above and further in view of Rockwell et al. (U.S. Pat. No. 5,840,301)

The teachings of Shitara et al. (EP '799), Shitara et al. (US '160), Kendall et al., Clauss et al., or Barleon et al. are as set forth above and differ from the invention as instantly disclosed in not specifically teaching humanized or chimeric anti-Flt-1 antibodies.

Rockwell et al. teach that chimerized, humanized, or single-chain antibodies may be used as functional equivalents to monoclonal anti-VEGF receptor antibodies, including anti-Flt-1 antibodies, providing binding characteristics are retained (see e.g. col. 7).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have made and used chimerized, humanized, or single-chain anti-Flt-1 receptor antibodies from the specific monoclonal antibodies of Shitara et al. (EP '799) or Shitara et al. (US '160) for use in the reagent and assays of Shitara et al. (EP '799) or Shitara et al. (US '160), as modified by Kendall et al., Clauss et al., or Barleon et al., because it was well known in the art that chimerized, humanized, or single-chain antibodies may be used as functional equivalents to monoclonal anti-Flt-1 antibodies from which they were derived providing binding characteristics were retained and one would have been motivated to substitute a functionally equivalent antibody in the reagent and assay in view of the direct suggestion in Rockwell et al. to do so.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Rockwell et al. (U.S. Pat. No. 6,448,077) also disclose anti-Flt-1 monoclonal antibodies (see e.g. col. 8).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

James L. Grun, Ph.D.
September 14, 2004

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
9/15/04